Dynamic kinetic and kinetic resolution of *N*-Boc-2-lithiopiperidine†

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Asymmetric substitution of 2-lithiopiperidines can be achieved by dynamic resolution; the organolithium is formed as a racemic mixture by proton abstraction (or tin–lithium exchange) and is resolved in the presence of a chiral ligand.

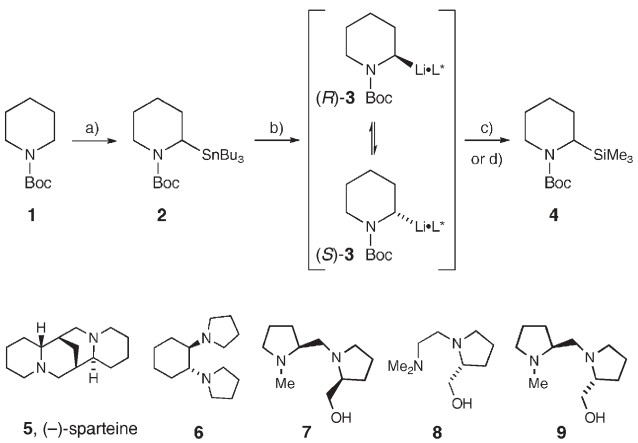
The formation and reaction of chiral organolithiums provides a valuable and stereoselective method for asymmetric synthesis.[1] Excellent selectivities have been achieved for the asymmetric deprotonation of a variety of substrates, an important example being *N*-(*tert*-butoxycarbonyl)pyrrolidine (*N*-Boc-pyrrolidine), in which the *pro-S* hydrogen atom at C-2 is removed with almost complete selectivity using *sec*-butyllithium and (−)-sparteine as the chiral base.[2] However, extension of this methodology even to the next higher homologue (*N*-Boc-piperidine) is problematic and occurs with low yields and low selectivities even after long reaction times.[3] Our recent success with the asymmetric *substitution* of *N*-Boc-2-lithiopyrrolidine,[4] in which the asymmetry arises not from a deprotonation but from the faster reaction of one of the diastereomeric chiral ligand complexes,[5] prompted us to attempt the resolution of the homologous 2-lithiopiperidine. Piperidines are one of the most important ring systems in natural products and medicinal compounds, and therefore selective and efficient methods for their synthesis are of widespread interest. We report the first highly enantioselective substitution of *N*-Boc-2-lithiopiperidine by a dynamic kinetic resolution.

Dynamic resolution of organolithiums can occur in the presence of a chiral ligand under either thermodynamic or kinetic control.[6] For a dynamic thermodynamic resolution, the diastereomeric organolithium complexes must be allowed sufficient time at an appropriate temperature to equilibrate to their thermodynamic ratio prior to quenching with the electrophile. If electrophilic quench is fast in comparison with equilibration then the enantiomer ratio (er) of the product is a reflection of the ratio of the diastereomeric organolithium complexes. However, in dynamic kinetic resolution, the electrophilic quench is slower than interconversion of the organolithium complexes and the enantiomer ratio of the product arises from the faster reaction of one of the complexes. Both possibilities should be explored for any particular chiral organolithium that is complexed with a chiral ligand.

Initially we began our study with the known racemic stannane **2**, prepared by proton abstraction of *N*-Boc-piperidine **1** using *sec*-butyllithium and the ligand tetramethylethylene diamine (TMEDA), followed by quenching with tributyltin chloride (Scheme 1).[7] We tested a variety of chiral ligands to effect the asymmetric substitution of the organolithiums **3**, generated from the racemic stannane **2** with *n*-butyllithium in Et_2O at −10 °C. Transmetalation was rapid at this temperature in the presence of the chiral ligands **5** or **6**, but TMEDA was added to enhance the rate of transmetalation prior to addition of the ligands **7–9** (which were pre-treated with *n*-butyllithium in Et_2O).[8]

To test for dynamic thermodynamic resolution, the organolithium·ligand complexes were allowed 1 h at −10 °C before cooling to −78 °C and electrophilic quench with trimethylsilyl chloride (TMSCl) (conditions c). The results for the different ligands are shown in Table 1. With the ligands (−)-sparteine (**5**) or the diamine **6**, the product **4** was formed essentially as a racemic mixture. Some selectivity was achieved using the ligands **7–9**, although the enantiomer ratio (er) was low. This was not improved by using longer reaction times or higher temperatures prior to cooling and quenching. The er of the product **4** was determined by chiral GC or by conversion of **4** to the corresponding *p*-bromobenzamide, followed by chiral HPLC, as reported.[3]

We then studied the dynamic kinetic resolution of the organolithiums **3** (Scheme 1, conditions d). The electrophile TMSCl was added slowly (over 40–50 min) at −10 °C and the results for the different ligands are shown in Table 1. The diamine



Scheme 1 Dynamic resolution of *N*-Boc-2-lithiopiperidine. a) *sec*-BuLi (1.2 equiv.), TMEDA (1.2 equiv.), Et_2O, −78 °C, 3.5 h, then Bu_3SnCl, 74%; b) *n*-BuLi (1.2 equiv.), Et_2O, −10 °C, 10 min, chiral ligand L* (1.5 equiv.) (ligands **7–9** were pre-treated with *n*-BuLi in Et_2O and with these ligands TMEDA was used to promote tin–lithium exchange); c) −10 °C, 1 h then −78 °C, 4.5 equiv. TMSCl; d) −10 °C, 2 min then 4.5 equiv. TMSCl in Et_2O added slowly over 50 min at −10 °C; see Table 1.

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Table 1 Formation of **4** by dynamic resolution using ligands **5–9**

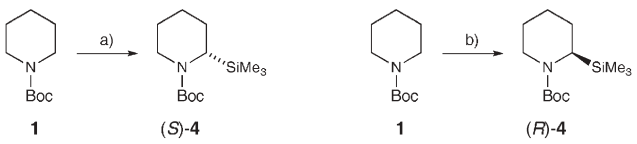
Entry	Ligand	Yield, er (R : S)[a] (DTR)[b]	Yield, er (R : S)[a] (DKR)[c]
1	**5**	86%, 55 : 45	55%, 53 : 47
2	**6**	88%, 50 : 50	86%, 51 : 49
3	**7**	46%, 23 : 77	45%, 72 : 28
4	**8**	39%, 59 : 41	60%, 11 : 89
5	**9**	41%, 58 : 42	62%, 7 : 93[d]

[a] The absolute configuration of the major enantiomer was determined by comparison with an authentic sample prepared according to ref. 3. [b] Dynamic thermodynamic resolution using conditions c) as described in Scheme 1. [c] Dynamic kinetic resolution using conditions d) as described in Scheme 1. [d] Yield at −20 °C was 71%, er 6 : 94.

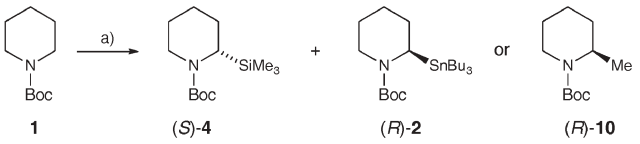
ligands **5** and **6** gave poor asymmetric induction. However the ligands **7–9** gave higher levels of selectivity. The ligand **7** is known to give good selectivity for the related dynamic kinetic resolution of *N*-Boc-2-lithiopyrrolidine.[4] By comparing entries 3–5 in Table 1, it is apparent that ligand **7** is the mismatched diastereomer in the resolution of *N*-Boc-2-lithiopiperidine. Excellent enantiomer ratios of the product **4** were obtained using dynamic kinetic resolution with the ligand **9** (a diastereomer of **7**). In this case, the diastereomeric organolithium complexes **3** can interconvert faster than electrophilic quench and one complex (the minor diastereomer based on the ratio obtained in the dynamic resolution under thermodynamic control with ligand **9**) reacts faster than the other.

An improvement to this procedure is to use direct proton abstraction of *N*-Boc-piperidine **1** to form the racemic *N*-Boc-2-lithiopiperidine. Using *sec*-BuLi, Et_2O and TMEDA followed by addition of the ligand **9** provides directly the diastereomeric complexes **3**. Addition of TMSCl then gave the desired product **4** (66%, er 92 : 8, S : R). We carried out some optimization of this dynamic resolution and found that the solvent THF gave slightly improved results (Scheme 2).‡ With chiral ligand **9**, the product (*S*)-**4** was formed with er 95 : 5. This is remarkable as THF often results in reduced levels of enantioselectivity in reactions of chiral organolithiums, and this has been ascribed to competition between THF and the chiral ligand for complexation to the lithium atom.[1] In our case, it is likely that the organolithium **3** complexed with the ligand **9** is considerably more reactive (to TMSCl) than any organolithium complexed with THF or TMEDA. As would be expected, the use of the enantiomeric ligand *ent*-**9**[8] gave the product (*R*)-**4**, with the opposite absolute configuration (Scheme 2).

We next probed the scope of the reaction with a variety of electrophiles. To our disappointment, slow quench at −20 °C of the organolithium **3** complexed with **9** using the electrophiles Bu_3SnCl, allyl bromide, DMF or Me_2SO_4 all resulted in products with little or no enantioselectivity. However, quenching with



Scheme 2 Dynamic kinetic resolution with ligands **9** and *ent*-**9**. a) *sec*-BuLi (1.2 equiv.), THF, TMEDA (1.2 equiv.), −78 °C, 3 h, then **9** (1.5 equiv.) (pre-treated with *n*-BuLi in Et_2O), then −20 °C, 2 min then 3–4 equiv. TMSCl added over 40–50 min at −20 °C, 60%, er 95 : 5, S : R; b) as a) but using *ent*-**9**, 58%, er 96 : 4, R : S.



Scheme 3 Kinetic resolution with ligand **9** and sacrificial electrophile TMSCl. a) *sec*-BuLi (1.2 equiv.), THF, TMEDA (1.2 equiv.), −78 °C, 3 h, then **9** (1.5 equiv.) (pre-treated with *n*-BuLi in Et_2O), then 2 equiv. TMSCl added over 1 h at −78 °C, then after 1 h Bu_3SnCl or Me_2SO_4; yield (*S*)-**4** 30–37%, er 75–80 : 20–25, yield (*R*)-**2** 12%, er 99 : 1 or yield (*R*)-**10** 19%, er 95 : 5, yield recovered **1** ~30%.

$PhMe_2SiCl$ gave *N*-Boc-2-(dimethylphenylsilyl)piperidine in reasonable yield and enantiopurity (58% yield, er 88 : 12). These results indicate that the enantioselectivity is dependent on the electrophile, as would be expected for a kinetic resolution, and more reactive electrophiles are less able to discriminate between the diastereomeric complexes.

As the reaction of the organolithium is highly selective with TMSCl, it is possible to use this as a sacrificial electrophile prior to addition of the desired electrophile. After some experimentation, it was found that best results were obtained by adding 2 equiv. of TMSCl slowly at −78 °C and leaving to stir for about 1 h prior to addition of the second electrophile (Scheme 3). This resulted in the formation of the product (*S*)-**4** (reduced amounts of TMSCl or shorter reaction times gave lower yields of **4** with high er) together with (*R*)-**2** or (*R*)-**10** (depending on the electrophile) and recovered piperidine **1**. As these reactions are conducted under kinetic (not dynamic) control, it is necessary to consume (*S*)-**3** prior to addition of the second electrophile. This limits the yield of the desired product (*R*)-**2** or (*R*)-**10**, but allows its formation with excellent levels of enantioselectivity (er up to 99 : 1).

Hence, high levels of enantioselectivity for either enantiomer of *N*-Boc-2-trimethylsilylpiperidine can be obtained by dynamic kinetic resolution of racemic *N*-Boc-2-lithiopiperidine in the presence of the chiral ligand **9**. This ligand does not, however, promote enantioselective dynamic kinetic resolution with a range of electrophiles, although TMSCl can be used as a sacrificial electrophile to promote enantioselective kinetic resolution. This chemistry could provide a solution to the poor levels of asymmetric induction obtained for the asymmetric deprotonation of *N*-Boc-piperidine, and could find use in the asymmetric synthesis of biologically active piperidine-containing compounds.

Notes and references

‡ General procedure: *N*-Boc-piperidine **1** (0.103 g, 0.55 mmol) and TMEDA (0.1 mL, 0.67 mmol) in THF (0.55 mL) were treated with *sec*-BuLi (0.51 mL, 0.67 mmol, 1.3 M in hexanes) at −78 °C. After 3 h, the deprotonated ligand **9** [prepared by adding *n*-BuLi (0.37 mL, 0.89 mmol, 2.4 M in hexanes) to **9** (0.165 g, 0.83 mmol) in THF (0.55 mL) at 0 °C] was added. The mixture was warmed to −20 °C and the electrophile TMSCl (0.32 mL, 2.5 mmol) in THF (0.32 mL) was added slowly over approximately 50 min. The mixture was quenched with MeOH (1.5 mL), the solvent was evaporated and the residue was purified by column chromatography on silica, eluting with light petroleum (b.p. 40–60 °C)–EtOAc (98 : 2) to give the piperidine (*S*)-**4** (85 mg, 60%), $[\alpha]_D^{24}$ +36.4 (1.95, $CHCl_3$), lit.[3] for (*R*)-**4**, er 73 : 27, $[\alpha]_D$ −16.0 (1.16, $CHCl_3$); other data as reported;[3] er 95 : 5 determined by GC [β-cyclodextrin-permethylated 120 fused silica capillary column 30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 psi, retention times 28.2 min (major) and 29.2 min (minor) (at 85 °C)] or by removal of the *N*-Boc group and conversion to the

p-bromobenzamide,[3] followed by chiral HPLC (Chiracel OD column, hexane–^{i}PrOH 99.5 : 0.5, flow rate 0.5 mL min^{-1}, detection at 254 nm, retention times: 26.8 min (major enantiomer (*S*)) and 27.9 min (minor enantiomer (*R*) – absolute configuration as reported[3])). The chiral ligand **9** can be recovered by column chromatography, eluting with CH_2Cl_2–MeOH (5 : 1), followed by evaporation of the solvent, acid/base wash (acidify with 2 M HCl, wash with EtOAc, basify with NaOH pellets and extract with EtOAc) and distillation under reduced pressure.

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8 Ligands **7–9** can be prepared readily in 2 steps (by coupling proline methyl ester with *N*-Cbz-proline followed by reduction) according to (*a*) T. Mukaiyama, *Tetrahedron*, 1981, **37**, 4111; (*b*) D. J. Gallagher, S. Wu, N. A. Nikolic and P. Beak, *J. Org. Chem.*, 1995, **60**, 8148.